# EXHIBIT B

**Objective:** With the post marketing use of gabapentin in patients other than with epilepsy it is important to identify whether these new populations may be particularly susceptible to specific adverse drug effects both labeled and unlabeled and to identify conditions under which specific adverse events may be more likely to occur in these new patient population. The development of the safety profile of any drug product is an evolving process. As with any marketed drug in order to provide guidance for the safe and judicious use of gabapentin for the specific clinical application which we are seeking in the United States (neuropathic pain), accumulation and analysis of the broader population's safety experience is critical for the ongoing development of an accurate safety profile. The intent of this review is to summarize the experience of the overall population using the ICH pharmacovigilance safety update report format with additional focused reviews of selected events for potential signals which might be of particular relevance to the neuropathic pain population. It should be noted that a dedicated Product Maintenance and Pharmacovigilance (PMP) committee for gabapentin will be formed to perform an on-going review of serious events on a periodic basis.

Report Format

I Overall Description of Postmarketing Dataset

A. **Section 1**

1. Total number of cases and events. Sources of report (reporter versus country of origin versus both). Gender distribution. Age breakdown. Serious cases. Outcomes. Breakdown by dose 0-2400, 2400-3600 and > 3600. Indications breakdown.

2. Table of body systems containing 2% or more (others can be included as "other") of the events with the most commonly reported events in each of those body systems in the text below the table

3. Table of those events reported in 2% or greater of events per case by COSTART Body System. Unlabeled events will be bold faced. Any unlabeled events will be reviewed in a general sense to see the nature of the events and whether they are consistent with the labeling. Sentence or two about the nature of events in off-label use. Breakdown by off label use. If we cannot get a summary table we can summarize the findings of the previous Periodic Safety Update Reports (PSUR).

4. Possibly provide a summary of events with a positive rechallenge by frequency.

Tables should combine WAERS and ARIS g reports

B. **Section 2**

This section will contain a table of events by Costart Body System reviewed in the 10 psurs and in all expert reports/pharmacovigilance assessment reports. Broken down by date of report, source of request in case of expert or pharmacovigilance reports. Summary of findings and current labeling status. The table will then be summarized in text below emphasizing the ongoing evaluation of cases in the database.

C. **Section 3**

Analysis of literature cases (brief summary of those cases with labeled events). Case summaries of those cases with unlabeled events. This is included based on the level of documentation and clinical detail usually required by the peer review process

D. **Section 4**

Review of fatal cases.

E. **Section 5**

Review of events of relevance to the neuropathic pain population. The intent would be to note whether there are possible signals of specific adverse events in the neuropathic pain population that may be diluted by the overall population and to assess the strength of any signal. A signal might be a positive rechallenge in the absence of risk factors and these cases if any would be summarized, otherwise a general overview would suffice with a conclusion based on medical review. The intent of the review of these events is to satisfy ourselves that the neuropathic pain population is not at an increased risk to develop these specific events.

Psychiatric (Nervous System)

Patients with chronic neuropathic pain may represent a population with a significant amount of comorbid depression (150 cases) and suicide (15). Therefore these cases will be looked at to include or exclude any significant signal of drug induced depression/worsening depression.

Cardiac

Heart failure and congestive heart failure (21) because of the high incidence of comorbid cardiovascular disease in the diabetic population.

Because of the high of incidence of peripheral edema in clinical trials of neuropathic pain and because it is one of the more commonly reported spontaneous events, this event may assume increased significance in patients with comorbid cardiovascular disease such as the diabetic population with neuropathic pain. Edema peripheral and peripheral edema will be looked at to see if there is an association with cardiovascular events and their sequelae. The intent of looking at these events is not to confirm or refute causality with gabapentin but to determine if edema and edema associated events may cause cardiovascular compromise in the neuropathic pain patient.

QT related events – Drugs from multiple therapeutic areas have been associated with QT interval prolongation and the neuropathic pain population would be expected to have significant comorbid cardiovascular disease, which might predispose patient to QT prolongation. Events to be looked at include cardiac arrest, ventricular fibrillation, heart arrest, QT interval prolonged, fibrillation ventricular, ventricular tachycardia.

Endocrine: Metabolic and nutrition

Diabetes Mellitus, diabetic coma, hyperglycemia, hypoglycemia, (70 cases) will be looked at. Do these cases generate a signal that gabapentin may effect glycemic control

Nervous

Addiction, drug dependence, withdrawal syndrome, (approximately 220 cases) will be looked at because it is a CNS active drug being used to treat a pain disorder.

Peripheral neuritis, neuropathy, neuralgia and polyneuritis will be looked at because gabapentin is a drug that effects nerves, and these patients have preexisting peripheral neuropathy which might may make them more susceptible to any drug induced peripheral neurotoxicity.

Urogenital events

Albuminuria, kidney failure, kidney function abnormal or nephrosis based on the strong association of diabetes with renal disease.

Special Senses

Retinal events. Association of diabetes with retinopathy

II. Drug Interaction

Focusing on interactions with oral sulfonlyureas, metformin, insulin, acarbose, thiazolidinediones, (hyperglycemia or hypoglycemia for these) antidepressants, steroids, analgesics, NSAIDS since these are the agents that would be expected to be used by neuropathic pain patients. In addition we would summarize drug interaction sections of 10 psurs.

III. Overdose

Overdose intentional, accidental, intoxication. Also summarize findings of 10 previous PSURs.

IV. Use in Pregnancy

Findings of previous PSURs plus case analysis

V. Children and Elderly

Will do a comparison table between elderly and all and children and all based on the differing age distribution between epilepsy, post-herpetic neuralgia and diabetic population. In order to do that we would need a table listing event frequency (≥ 2% of children and all cases). We will make note of any event reported with a greater proportionate frequency ≥ 3:1 ratio in either special population when compared to the over all population. Another alternative would be to list the 10 most frequently reported events in the special populations compared to the overall population and then make a statement as to whether or not they are labeled or unlabeled. Any signals from 10 PSURs will be noted.